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Influence of Infectious Disease on Ceftiofur Pharmacokinetics and the relative risk of violative residues in cattle

Sarah Higgins

Abstract

Mastitis is a growing problem that is occurring with cattle in the United States, and it is primarily a debilitating problem for the dairy industry. As the demand for these products grows, the number of large herd sizes has been increasing. It is a very debilitating disease that causes inflammation of the mammary tissue that can cause permanent damage to the animal and cause it to become unproductive. This disease can be spread through cross-contamination of milking equipment because of its bacterial origin, wreaking havoc throughout a herd quickly. A common antibiotic for the treatment of this disease is Ceftiofur. It is revered for being a safe antibiotic that minimizes withdrawal time and leaves no milk residue, therefore reducing milk waste. Recently, society has become more aware of agricultural practices, and antibiotic residues in animal products are becoming a hot topic across many social groups. Studies are being done to look deeper into the issue and look at differences between the pharmacokinetics of a diseased animal when compared to a healthy one.

Introduction

Antibiotics are an incredibly valuable asset to the livestock industry to manage and treat bacterial infections, and a common one of these is Ceftiofur. This particular medication is a beta-lactamase, broad spectrum, third-generation cephalosporin antibiotic. It works by binding and inactivating penicillin-binding proteins, also known as PBPs, which are located on the inner membrane of a bacterial cell wall. When the antibiotic inactivates these proteins, it interferes with the cross-linking of peptidoglycan that is necessary for the bacterial cell wall (Ceftiofur). The

interference causes a weakening of the cell wall and the cell is lysed (Ceftiofur). There are a couple of different forms of this antibiotic including Ceftiofur hydrochloride and Ceftiofur sodium. Ceftiofur hydrochloride, for example, Excenel®, can be used to treat different bacterial diseases across several species, but in cattle, it is indicated to be used in the treatment of bovine respiratory disease, shipping fever, pneumonia that are associated with the bacteria *Mannheimia haemolytica*, *Pasturella multocida*, and *Histophilus somni* (Zoetis, 2013). It can also be used in the treatment of acute interdigital necrobacillosis, also known as foot rot and is another

common occurrence in the cattle industry. It is best used for foot rot when it is associated with the bacteria *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* (Zoetis, 2013). Ceftiofur hydrochloride is also used in the treatment of acute metritis (Zoetis, 2013), which can happen up to 14 days postpartum generally. According to label direction, cattle that are treated with Excenel® should not be taken to slaughter for four days after the last treatment with the drug, however, there is not any evidence of milk residues and there should not be any milk loss resulting from the drug being used with dairy cattle (Zoetis, 2013).

There is another form of Ceftiofur that is known as Ceftiofur sodium, which has a broader species spectrum than the Ceftiofur hydrochloride mentioned previously. Along with cattle and swine, this antibiotic has equine, canine, and ovine uses. A commercial example of this is Naxcel®. Recently, consumers have become more concerned about the presence of antibiotics in their meat and dairy products. This ever-growing fear of contaminated food has sparked an interest in making sure that the animal products produced by the agricultural industry are indeed safe for consumption. A critical step in food safety is that if an animal is treated with medication, that the producer follows an appropriate withdrawal time that is required for the medication to leave the animals

system entirely. In the case of Ceftiofur sodium, when used in cattle, there is not a specified withdrawal time when it is used according to label directions; in fact, Naxcel is self-proclaimed to be the first antibiotic with “zero milk discard.” (Naxcel (Ceftiofur Sodium) sterile powder). The lack of a withdrawal time is true for both slaughter cattle as well as dairy cattle. However, many of the studies that have looked into the elimination kinetics of Ceftiofur have used healthy animals for their experiments. It is important to note because animals clear drugs from their systems differently when they are diseased versus when they are healthy. The instances of Ceftiofur being the cause of violative residues in cattle have been on the rise and are becoming a more significant cause for concern within the livestock community, with violations in both meat and milk. Pharmacokinetics looks into how drugs move through the body (Mochel, 2018). It is a process by which a drug is absorbed, distributed, metabolized and excreted from the body. The concentrations of these drugs are generally measured in the blood plasma, which provides an average drug exposure from the entire body (Mochel, 2018). The liver and kidney are critical organs in the clearance of medications from the body. Drugs with a low FU (fraction of drug unbound in the plasma) tend to be cleared by the liver while drugs with a high FU tend to be cleared by

the kidney (Mochel, 2018). A common issue in the cattle industry, especially with dairy cattle, is animals being infected with mastitis. Mastitis is an inflammation of the mammary gland that is usually a response to a bacterial infection. The inflammation response causes the mammary tissues to be damaged that can become permanent without treatment (Dairy, 2018). This disease can cause a financial impact on producers because of its reduction in milk yield and it causing an increase of cull rates because of damage to the tissues from the disease making the animals no longer productive (Dairy, 2018). Several studies that have been used in this review look further into the clearance of Ceftiofur from diseased cattle, and to further investigate the differences in clearance of this antibiotic in a diseased bovine when compared to a healthy animal.

Discussion

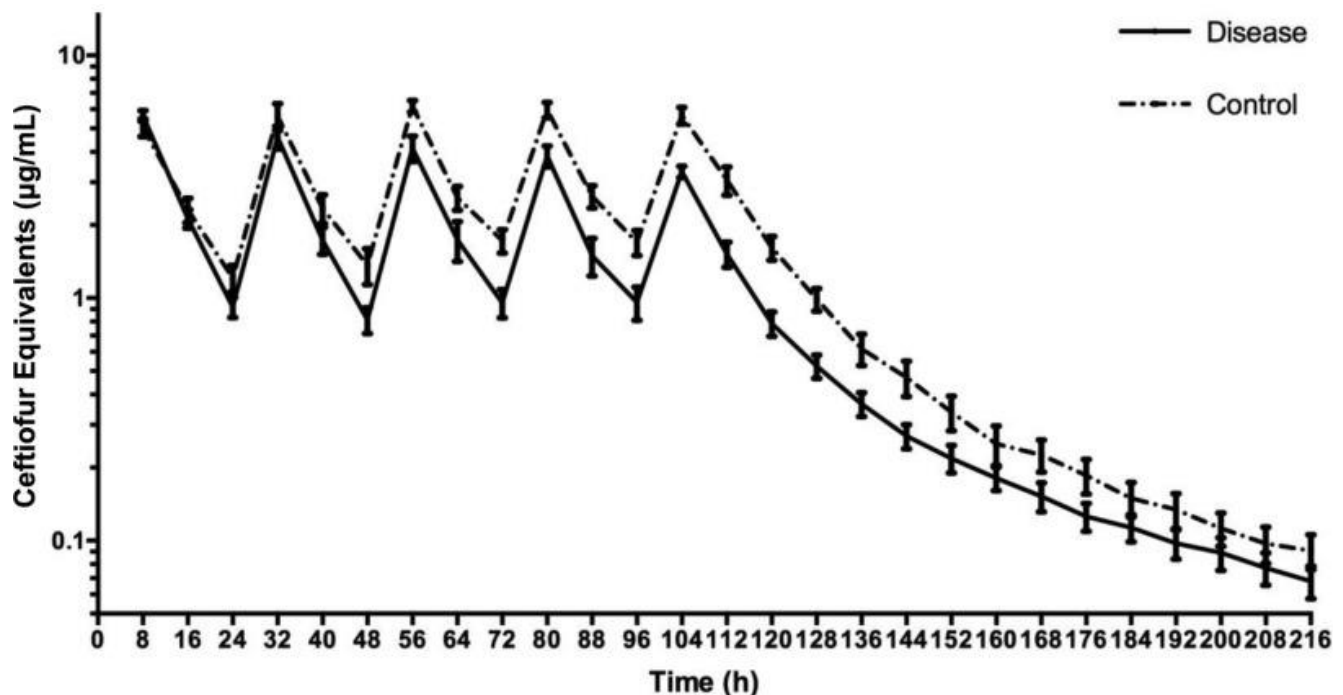
The consumer demand for dairy products has been on the rise, and in the past several years, the United States dairy industry has gone through a variety of changes to compensate for growing demand. One of these changes is that the number of larger herds across the country. In a study performed in 2013, they looked at 50 farms to characterize clinical mastitis that occurs in large dairy herds in Wisconsin (Oliveira, Hulland, & Ruegg, 2013). To participate in this study, the herd was required to have a minimum of 200 lactating cows, to

participate in monthly DHI testing, they were required to use a computerized system for record keeping, use a specific milking routine that included fore-stripping quarters for mastitis detection, and they had to use antimicrobial pharmaceuticals for treatment of infected cows (Oliveira, Hulland, & Ruegg, 2013). If a farm met all of these criteria, staff participating in the study then visited the farm, and each farm was instructed to enroll the next 17 cows that presented with clinical mastitis in their herd. When looking at presenting cows, they did not discriminate between levels of severity of the disease. As soon as cows presented with mastitis, they were given treatment and milk samples were collected from presentation until 14 to 21 days after the treatment ended. The samples were taken from each infected quarter of the mammary gland and then used for microbiological analysis. The treatments prescribed to the animals were based on individual farm protocol that was already in place. After treatment was ended, they took follow up data until 90 days after enrolment. The collected milk was analyzed for the presence of microbial pathogens, and out of the 741 cases analyzed, the most common pathogens were *Escherichia coli*, which was present in 22.5% of the cases. The second most common was an environmental streptococcus, which was present in 12.8% of the cases (Oliveira, Hulland, & Ruegg, 2013). The study concluded that environmental pathogens are one of the major causes of clinical mastitis in dairy cattle. By looking at milk and bacterial analysis, they determined that the characteristics and clinical

outcomes of animals presenting with this disease were mostly dependent on the disease-causing pathogen. Roughly 30% of the collected samples resulted in no microbial growth. It was stated that more studies need to be conducted in order to understand further and better manage these cases. Through bacterial analysis, it was also found that *Staphylococcus aureus* was not a significant contributor to clinical cases of mastitis in Wisconsin because there were only a few cases that isolated this organism. While doing the 90-day follow-up, it was observed that cattle that experienced disease due to gram-negative bacteria were more likely to revert to a disease state from mastitis. One-third of these animals infected with the gram-negative organisms were affected by severe symptoms. Animals that were infected with gram-positive bacteria were more likely to have mild to moderate symptoms. (Oliveira, Hulland, & Ruegg, 2013). The overall goal of this study was to

understand better which specific pathogens caused different levels of disease to understand better and set up more pathogen-specific treatment programs. (Oliveira, Hulland, & Ruegg, 2013)

Dr. Patrick Gorden has made several contributions to this area of research, with mastitis of dairy cattle being his disease model of choice. In a study performed in 2016, Dr. Gorden and his fellow researchers had a hypothesis that disease plays a role in the pharmacokinetics of Ceftiofur hydrochloride (CEF) and was a cause of the violative residues being found upon inspection. Dr. Gorden and a team took eight cows with naturally occurring mastitis and eight clinically healthy cows from the Iowa State University dairy farm. They treated both the control and the diseased group with 2.2 mg of Ceftiofur hydrochloride per kilogram of body weight once a day for five consecutive



(Gorden P. J., et al., 2016)

days by intramuscular administration. They then collected blood from the animals at time points 0, 0.33, 0.67, 1, 1.5, 2, 3, 4, 8, 16 and 24 hours after the first injection of the CEF. They also took samples every eight hours afterward until 120 hours after the final dose of the antibiotic. The plasma was separated from the blood sample and was analyzed by liquid chromatography along with mass spectrometry looking at CEF concentrations. At every time point, except for zero, the team was able to detect Ceftiofur hydrochloride in the plasma samples. They found that the plasma harvested from the diseased group of cattle contained a much higher concentration of CEF in their plasma after the first injection, and then a lower concentration from hours 40-152 after the first administration of Ceftiofur. These results were put into a single-dose noncompartmental PK model, which indicated that the diseased group had a shorter plasma half-life. When the diseased cattle were compared to the control cattle, it was found that the diseased group initially had a higher peak concentration and a higher volume of distribution and drug clearance rates. The plasma obtained from the diseased group of cattle also showed a lower area under the curve per dosing interval, a steady-state concentration maximum, and dose-adjusted peak steady-state concentration. When compared to the control group, it was determined at all

other PK parameters were the same between the two groups. It was concluded that altered pharmacokinetics could be playing a role in the differences between the plasma concentrations between the two groups. This alteration could be causing an issue of violative residues in meat, but more research was needed to make a reliable connection between the two. (Gorden P. J., et al., 2016)

This research led to a study performed in 2017, also by Dr. Gorden, that looked at the pharmacokinetics of Ceftiofur hydrochloride when given with flunixin meglumine, more commonly known as Banamine. Flunixin meglumine is a very common nonsteroidal anti-inflammatory medication (NSAID) that is used in both cattle and horses. It is used to reduce fevers and inflammation that occur with a variety of conditions (Merck Animal Health, 2018). There is a withdrawal time for flunixin. The label states that cattle should not be slaughtered for consumption within four days of the animal's last treatment. In dairy cattle, milk from a treated animal must not be used for human consumption until 36 hours after the last treatment (Merck Animal Health, 2018). Banamine and Ceftiofur are both approved for use in dairy and beef cattle, and in conjunction with each other during treatment (Gorden P. J., et al., 2017). Interestingly enough, both Ceftiofur and Banamine are the

most popular drugs of choice from their respective drug categories (Gorden P. J., et al., 2017). This study was interested in determining if the pharmacokinetics of flunixin meglumine, when administered intravenously, or Ceftiofur hydrochloride, when administered intramuscularly, would show different pharmacokinetics when administered in conjunction compared to when they are administered as individual doses. For their treatment groups, ten healthy cows from the Iowa State University dairy farm were utilized; they did not have a disease group for this experiment. The study used a three-period, three-treatment crossover design. All the cows were given each medication on time and were then given a ten-day washout period between the treatments. After the treatment period ended, samples of plasma and interstitial fluid were taken and stored for analysis. Plasma microfiltrate was also collected from each cow and was then put through microcentrifugation to look at the plasma protein binding of each of the medications. To determine drug concentrations in the samples, they were analyzed using high-pressure liquid chromatography, which was coupled with mass spectrometry. The results showed that when flunixin and Ceftiofur are co-administered, interactions between the two do not occur. Dr. Gorden concluded in his paper that more studies need to be done to determine further if these

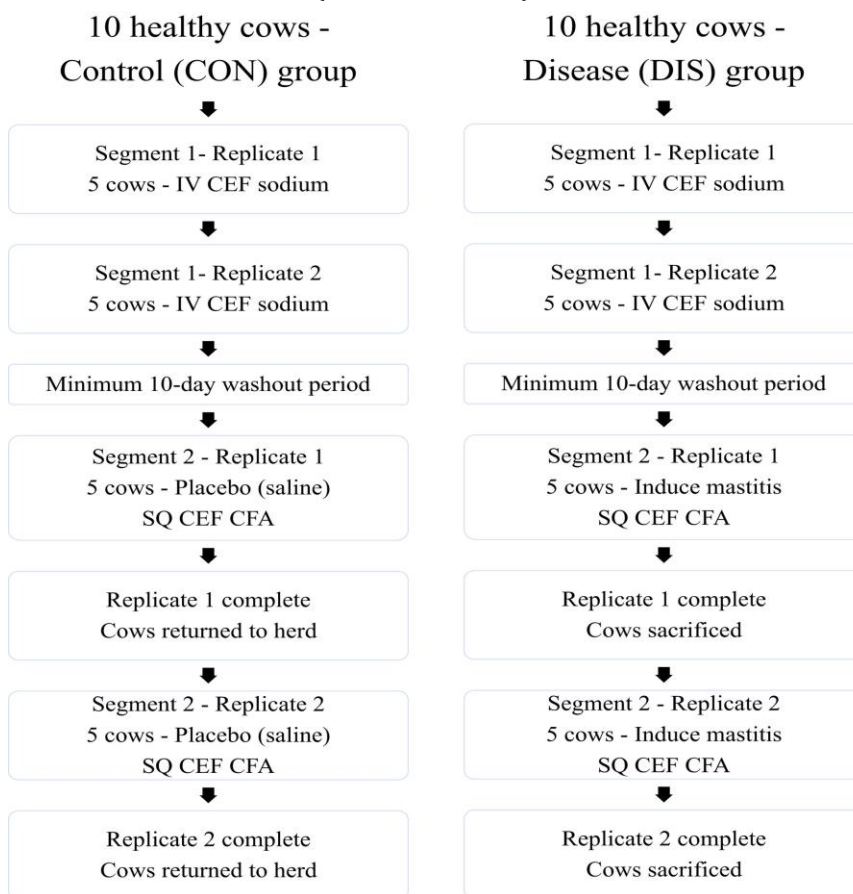
results are still valid in cattle infected with a disease (Gorden P. J., et al., 2017). This goes back to the previous study performed in 2016 that indicated that cattle in a diseased state have altered pharmacokinetics and pass drugs out of their system at a different rate (Gorden P. J., et al., 2016).

Following the 2017 study, Dr. Gorden recently published another study this year that looked into comparing the plasma and interstitial fluid pharmacokinetics and tissue residues of cattle infected with coliform mastitis that were treated with Ceftiofur crystalline-free acid. There were several objectives that the team set to accomplish in this study. The first was to determine the absolute bioavailability of Ceftiofur crystalline-free acid (CFA) in healthy cows when compared to cattle that were diseased. They also compared the plasma and interstitial fluid pharmacokinetics and plasma protein binding of the drug between the two groups of cattle. The last goal of the study was to determine the Ceftiofur residue profile in tissues of diseased cattle (Gorden, et al., 2018). Unlike the study performed in 2016, which had cattle collected with naturally occurring mastitis (Gorden P. J., et al., 2016), the cattle for this study that were selected for the disease group were induced with mastitis using an intramammary *Escherichia coli* infusion (Gorden, et al., 2018). After mastitis was induced,

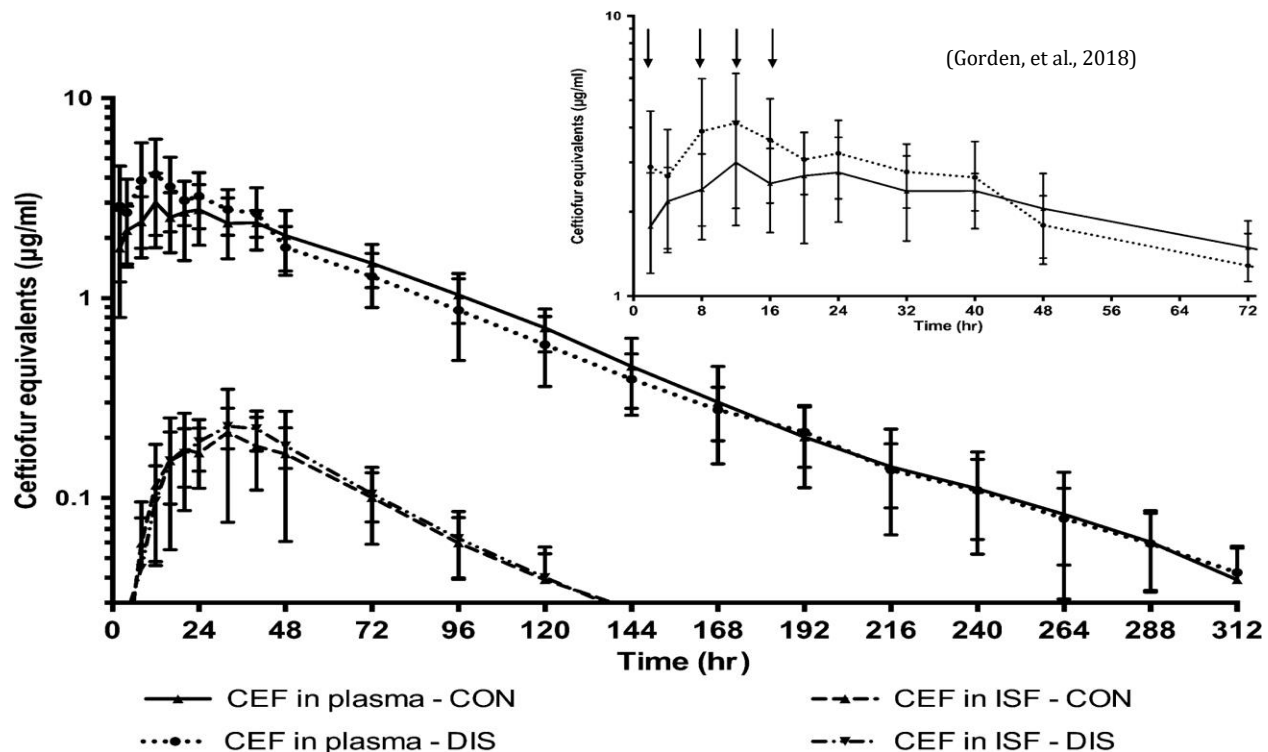
the cattle were treated with Ceftiofur CFA. It was found that there was not a significant effect of treatment, but the treatment-by-time interaction was significant. There was a much higher concentration of the drug in the plasma of the diseased cows at the T2 hour, T12 and T16. For the diseased cows, an analysis showed that the terminal half-life was much longer when compared to a healthy group as well as the volume of distribution

during the elimination of the drug was much higher in the diseased cows. The results also showed that there was no difference in the plasma protein binding of Ceftiofur and interstitial fluid pharmacokinetics (Gorden, et al., 2018).

Another difference with this study, when compared to the 2016 paper, was that the cattle used in this experiment were sacrificed at the end of the trial. The kidneys of the sacrificed animals showed that none of the cattle had any residues of Ceftiofur in their kidney that was above the stated tolerance level in the United States (Gorden, et al., 2018).



The kidneys were studied after the animals had gone through a required withdrawal period. Upon talking to Dr. Gorden, he stated that he wishes that they had sacrificed the cattle used in the previous study to look at residues in the inner organs. The cattle in that study were much sicker than these cattle, and he thinks that the results would have been fascinating. The 2018 study concluded that the results did not support their hypothesis that diseased cattle needed a longer withdrawal time after treatment with Ceftiofur; however, there were alterations in the terminal half-life of the drug that suggests this idea is theoretically possible (Gorden, et al., 2018).



There was a study performed in 2002 that looked into the efficacy of intramuscularly administered Ceftiofur to lactating dairy cows with clinical mastitis, to reduce the incidences of mastitis related death and culling. They took 104 dairy cows that were diagnosed with clinical mastitis and randomly assigned the cows to two different treatment groups. In one group, the cows were given 2.2mg/kg of Ceftiofur through an intramuscular injection. This dosage was repeated every 24 hours for five doses of the drug. The second group of cows was the control group and did not receive any antibiotic intervention of their disease. However, both treatment groups did receive an intramammary injection of pirlimycin (Erskine, Bartlett, VanLente, & Phipps, 2002). Pirlimycin hydrochloride is used for the

treatment of clinical and subclinical mastitis in lactating cattle. It is used in response to mastitis caused by *Staphylococcus* and *Streptococcus* bacteria. This antibiotic is the only FDA-approved antibiotic on the market that is approved for treating mastitis. (Zoetis Services LLC, 2018). The Pirlimycin was given in each mammary quarter every 24 hours for three doses. It was also noted that each cow in the trial was initially given fluids and anti-inflammatory drugs as supportive therapies and these therapies varied from farm to farm. The anti-inflammatory used was flunixin meglumine, also known as Banamine. At the conclusion of the study, it was determined that 14 out of 104 cases (13.5%) the cow ended up either dying or was culled. Out of 51 cows that were treated with Ceftiofur, 4 of them or 7.8% were lost (Erskine, Bartlett, VanLente, & Phipps,

2002). 53 cows were not treated with antibiotics and out of those ten were lost. 56 cows were positive for a coliform organism upon culture, and it was found that those cases produced a higher loss rate than the cows that were not infected with a coliform organism (Erskine, Bartlett, VanLente, & Phipps, 2002). Out of the infected 14 of the animals were lost when compared to the zero that was lost out of the 48 unaffected animals. When looking into the treated versus control groups, however, there were 27 cows in the control group that were affected with coliforms, and 10 of them were considered lost because of death or culling. In the treated group, there were 29 animals infected with coliform organisms, and four of them were considered losses (Erskine, Bartlett, VanLente, & Phipps, 2002). After analysis of the results, it was concluded that an intramuscular injection of Ceftiofur did not affect the outcome of cattle infected with severe clinical mastitis when all etiologic, or disease-causing factors, were included in the analysis. They did, however, conclude that when a dairy cow suffers from severe clinical mastitis as the result of coliform organisms, that therapy with Ceftiofur reduced the proportion of cases that resulted in the loss of an animal from either death or culling (Erskine, Bartlett, VanLente, & Phipps, 2002).

Conclusion

Mastitis is a growing problem that is occurring with cattle in the United States, and it is primarily a debilitating problem for the dairy industry. As the demand for these products grows, the number of large herd sizes has been increasing. It is a very debilitating disease that causes inflammation of the mammary tissue that can cause permanent damage to the animal and cause it to become unproductive. This disease can be spread through cross-contamination of milking equipment because of its bacterial origin, wreaking havoc throughout a herd quickly. A common antibiotic for the treatment of this disease is Ceftiofur. It is revered for being a safe antibiotic that minimizes withdrawal time and leaves no milk residue, therefore reducing milk waste. Recently, society has become more aware of agricultural practices, and antibiotic residues in animal products are becoming a hot topic across many social groups. Studies are being done to look deeper into the issue and look at differences between the pharmacokinetics of a diseased animal when compared to a healthy one. These studies primarily looked at Ceftiofur because of its common usage and overall safety claim. Previously, safety studies of this antibiotic were performed using healthy cattle, and because animals in a diseased state excrete pharmaceuticals differently, it was essential to include animals

infected with a disease. By looking at plasma and other biological samples, it was determined that although the idea that Ceftiofur can be excreted slower from a cow infected with mastitis increasing the frequency of violative residues, the results did not show a prominent difference between healthy cows and those infected with mastitis. More studies need to be performed in the future to look further into this issue. It is also essential to further investigate how other antibiotics work in this model system including diseased cattle. Although most violations in cattle are the result of Ceftiofur residues, with the ever-growing trend of society being concerned about antibiotics in their food, it would be interesting to look more into other common antibiotics. Also, Ceftiofur is not only used in dairy cattle. It is also critical for therapy of swine, beef cattle, sheep, and horses. Although horses are not used as a meat source in the United States, it would be interesting to look into the elimination kinetics of horses as well as the other species it is approved for. Looking at residues in more species would give a broader idea of safety across species barriers and give a broader picture of the residues left behind from Ceftiofur in food animals.

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